PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CLEV200023PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/21487	International filing date *(day/month/year)* 01 July 2004 (01.07.2004)	Priority date *(day/month/year)* 12 September 2003 (12.09.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 38/00, 38/36; C07K 4/12, 14/745 and US Cl.: 530/300, 345		
Applicant CLEVELAND STATE UNIVERSITY		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 April 2005 (12.04.2005)	23 March 2006 (23.03.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer: Lori B. Barnhart Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on:
   - ☐ the international application in the language in which it was filed.
   - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
     - ☐ international search (under Rules 12.3 and 23.1(b))
     - ☐ publication of the international application (under Rule 12.4(a))
     - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
   - ☐ the international application as originally filed/furnished
   - ☒ the description:
     pages 1-49 as originally filed/furnished
     pages* NONE received by this Authority on _____
     pages* NONE received by this Authority on _____
   - ☒ the claims:
     pages 51-60 as originally filed/furnished
     pages* NONE as amended (together with any statement) under Article 19
     pages* 50, 61, 61a, 61b received by this Authority on 15 September 2005 (15.09.2005)
     pages* NONE received by this Authority on _____
   - ☒ the drawings:
     pages 1-21 as originally filed/furnished
     pages* NONE received by this Authority on _____
     pages* NONE received by this Authority on _____
   - ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages _____
   - ☐ the claims, Nos. _____
   - ☐ the drawings, sheets/figs _____
   - ☐ the sequence listing (*specify*): _____
   - ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages _____
   - ☐ the claims, Nos. _____
   - ☐ the drawings, sheets/figs _____
   - ☐ the sequence listing (*specify*): _____
   - ☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9,11-42,50 and 52-111

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 9,11-42,50 and 52-111

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 2-5, 112-135	YES
	Claims 1, 6-8, 10, 43-49, 51	NO
Inventive Step (IS)	Claims 2-5, 112-135	YES
	Claims 1, 6-8, 10, 43-49, 51	NO
Industrial Applicability (IA)	Claims 1-8, 10, 43-49, 51, 112-135	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1, 6-8, 10, 43-49, and 51 lack novelty under PCT Article 33(2) as being anticipated by Hortin (1990). The claims are drawn to peptides having a specific sequence that is identical to a portion of human Factor Va. In some dependent claims, this sequence is DYDY or DYDYQ. In some dependent claims, the peptide is claimed to demonstrate a specific level of inhibition of Factor Va. Some dependent claims are drawn to compositions comprising said peptide and analogues that mimic said peptide. In some dependent claims, various tyrosine (Y) residues are sulfonated.

Hortin (1990) teaches fragments of Factor Va comprising the sequence DYDYQ in which various Y residues are sulfonated (Figure 6, p. 950). Because Claim 1 recites "a peptide having a sequence identical to SEQ ID NO:10", it is interpreted as being broadly drawn to any peptide having the sequence DYDY, which includes Factor Va itself. In other words, claim 1 can be interpreted as being drawn to Factor Va, which is not novel.

Claims 2-5 and 112-135 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest peptides with specific activities against Factor Va activity, i.e. IC_{50} values.

Claims 1-8, 10, 43-49, 51, and 112-135 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Applicant's comments regarding the Hortin reference regarding claims 1, 6-8, 10, 43-49, and 51 are noted. At the heart of these comments is the definition of the word "peptide" and the teachings of Hortin as they pertain to sequence data. Applicant alleges that "Hortin entirely fails to identify any specific sequence of amino acids in any region of factor Va that are responsible for inhibiting the generation of thrombin," but this observation is immaterial to the novelty of the cited claims. Claims 1, 6-8, 10, 43-49, and 51 are broadly drawn to any peptide comprising several particular short sequences, i.e. full-length Factor Va. Claims 43-48 require that the composition comprise such a peptide and be "adapted for inhibiting thrombin generation," but the claim does not point out the manner of such an adaptation or the extent of inhibition required. Similarly, the term "analogue" is not particularly defined in the specification, so any compound that has any functions or structural similarity to the peptide of claim 1 would be considered an "analogue." Applicant's points regarding the definition of "peptide" are noted, but the term is not particularly defined in the specification as "at most up to about 50 amino acids."

The examiner agrees that new claims 112-135 are not anticipated by Hortin.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 10, 51, 115, 119, 127, and 135 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s):

Claims 10, 51, 115, 119, 127, and 135 recite a peptide "analogue" that "mimics" the peptide of claims 1 and 43, respectively, but they do not particularly point out what characteristics are being "mimicked" by the "analogue". For example, the analogue could mimic the sequence, structure, function, or some other property of the peptide of claims 1 and 43. Additionally, it is not clear to what class of chemical "analogue" refers.

Applicant alleges that the terms "mimics" and "analogue" ARE defined at page 17, lines 7-21, of the present application, but this cited passage merely describes the putative functions of analogues and provides several examples of analogues. No particular definition of "mimics" is provided. The specification provides no criteria by which a person of ordinary skill in the art could determine whether a given compound is an analogue of the claimed peptides.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ on paper

   ☒ in electronic form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto which form part of the basis of the report, may be marked "superseded."*

CLAIMS:

1. A peptide having a sequence of amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va.

2. The peptide of claim 1 wherein the peptide exhibits an IC_{50} of less than about 100 μM, the IC_{50} being the amount of the peptide that inhibits 50% of the activity of human factor Va.

3. The peptide of claim 2 wherein the peptide exhibits an IC_{50} of less than about 15 μM.

4. The peptide of claim 3 wherein the peptide exhibits an IC_{50} of about 1.6 μM.

5. The peptide of claim 4 wherein the peptide exhibits an IC_{50} of about 500 nM.

6. The peptide of claim 1 wherein the peptide comprises the amino acid sequence DYDY.

7. The peptide of claim 1 wherein the peptide comprises the amino acid sequence DYDYQ.

8. A pharmaceutical composition comprising the peptide of claim 1.

9. A method for treating human subjects having blood clotting disorders, the method comprising administering the pharmaceutical composition of claim 8 to the human subjects.

10. A peptide analogue that mimics the peptide of claim 1.

107. The method of claim 106 wherein the amino acid sequence is DY(-SO_3)DY(-SO_3)Q.

108. The method of claim 102 wherein the effective amount of the peptide is in the range of from about 0.01 to 1000 mg/kg of body weight, per day.

109. The method of claim 108 wherein the effective amount of the peptide is in the range of from about 0.1 to 100 mg/kg of body weight, per day.

110. The method of claim 109 wherein the effective amount of the peptide is in the range of from about 1 to 10 mg/kg of body weight, per day.

111. A method for inhibiting thrombin generation in a patient suffering from a blood coagulation disorder, the method comprising:

administering to the patient an effective amount of a peptide that mimics the peptide of the method of claim 102.

112. A peptide consisting of a sequence of four amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 698 (SEQ ID NO. 10) of the human blood clotting factor Va.

113. The peptide of claim 112 wherein the peptide comprises the amino acid sequence DYDY.

114. A pharmaceutical composition comprising the peptide of claim 112.

115. A peptide analogue that mimics the peptide of claim 112.

116. A peptide consisting of a sequence of five amino acids which is identical to a sequence of consecutive amino acids found within amino acids 695 to 699 (SEQ ID NO. 11) of the human blood clotting factor Va.

117. The peptide of claim 116 wherein the peptide comprises the amino acid sequence DYDYQ.

118. A pharmaceutical composition comprising the peptide of claim 116.

119. A peptide analogue that mimics the peptide of claim 116.

120. A pharmaceutical composition adapted for inhibiting thrombin generation, the composition comprising a peptide consisting of an amino acid sequence DYDY (SEQ ID NO. 10).

121. The pharmaceutical composition of claim 120 further comprising a carrier.

122. The pharmaceutical composition of claim 120 wherein one of the Y amino acids of the amino acid sequence is sulfonated.

123. The pharmaceutical composition of claim 122 wherein the amino acid sequence of the peptide is DY(-SO_3)DY.

124. The pharmaceutical composition of claim 122 wherein the amino acid sequence of the peptide is DYDY(-SO_3).

125. The pharmaceutical composition of claim 120 wherein both of the Y amino acids of the amino acid sequence are sulfonated.

126. The pharmaceutical composition of claim 125 wherein the amino acid sequence of the peptide is DY(-SO_3)DY(-SO_3).

127. A pharmaceutical composition comprising a peptide analogue that mimics the peptide of the composition of claim 120.

128. A pharmaceutical composition adapted for inhibiting thrombin generation, the composition comprising a peptide consisting of an amino acid sequence DYDYQ (SEQ ID NO. 11).

129. The pharmaceutical composition of claim 128 further comprising a carrier.

130. The pharmaceutical composition of claim 128 wherein one of the Y amino acids of the amino acid sequence is sulfonated.

131. The pharmaceutical composition of claim 130 wherein the amino acid sequence of the peptide is DY(-SO_3)DYQ.

132. The pharmaceutical composition of claim 130 wherein the amino acid sequence of the peptide is DYDY(-SO_3)Q.

133. The pharmaceutical composition of claim 128 wherein both of the Y amino acids of the amino acid sequence are sulfonated.

134. The pharmaceutical composition of claim 133 wherein the amino acid sequence of the peptide is DY(-SO_3)DY(-SO_3)Q.

135. A pharmaceutical composition comprising a peptide analogue that mimics the peptide of the composition of claim 128.